The human airway epithelia represent the first line of defense against invading pathogens and environmental stressors in the lung. However, often the exposure of airway epithelia to these stress factors disturbs cellular homeostasis (stress) and leads to activation of the stress response pathways. These pathways serve primarily as a cellular adaptation mechanism to alleviate stress, but if the stress persists or the recovery mechanisms are defective, the stress response leads to cell death.

Thus, dysregulation of stress response pathways in human airway epithelia cells contributes to severity of many human diseases including lung cancer, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF).

Hence, cellular stress responses play important roles in gene expression regulation under both physiological and pathological conditions. The extent and specificity of these processes are not clear. Although to date considerable progress has been made towards understanding the cellular pathways underlying the cellular stress response, the significance and mechanisms of actions of related short noncoding RNA- micro-RNAs (miRNAs), are poorly understood. Most of the current information available is steady-state analysis, whereas we suggest that what is truly needed is a dynamic/temporal analysis of the stress induced miRNA profiles and we propose to study this in the present proposal.

The overall goal of this proposal is to determine the role of micro-RNAs (miRNAs) in the stress-induced response pathways in human airway epithelia.

Our hypothesis is that during adaptive phase of stress response, specific miRNAs levels are changed to either restore cellular homeostasis or target the cells for apoptosis. If the cell cannot restore homeostasis, the miRNA expression profiles are changed to quickly target cells for apoptosis. Furthermore, the stress response pathway can also be regulated by another class of miRNA, the "dynamic" miRNAs. We hypothesize that "dynamic" miRNAs have both pro-adaptive and pro-apoptotic functions that depend on their expression levels during the stress response time course.

Thus, we hypothesize that the "dynamic" miRNAs are the critical regulators for controlling the switch from adaptation to apoptosis during the stress, and thereby they determine the cell fate.

To test this hypothesis, we propose to examine the poorly characterized molecular mechanisms by which the cellular stress responses governs miRNAs expression and to identify the biological roles and significance of miRNAs in this process.

The miRNA component of cellular stress response pathway has potentially far-reaching implications in a number of human diseases including cancer, neurological, pulmonary and cardiovascular diseases.

Given the exciting potential of using miRNA mimics or antagonists in regulating this pathway and more importantly, in future therapies, understanding the role of miRNAs in various disease states is both critical and significant.